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Review

Research progress on the treatment of spinal cord injury with cellular transplantation ☆

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Abstract

Spinal cord injury(SCI) is a severe trauma to the central nervous system(CNS). This article reviews recent advances in cellular transplantation to treat SCI. Transplanted cells can supply new neurons to replace injured ones, promote regeneration of axons and myelin sheath, modulate the inflammatory response, and thus promote recovery from traumatic injury of the CNS. Cellular transplantation is a promising potential method for the treatment of SCI.

Keywords: transplantation; Stem cells; Schwann cells; olfactory unsheathing cells; axon

ITRODUCTION

Spinal cord injury(SCI) is a severe trauma to the central nervous system, which is often characterized by immediate and irreversible loss of sensory and motor functions below the level of the injury. The treatment of SCI continues to be a challenging problem for scientists and clinicians. In the past it was believed that axons were not capable of regeneration after transection, but recent advances in the use of cellular transplantation to promote recovery from traumatic injury of the CNS have changed this notion. Repair after SCI includes four areas: ①cell survival; ②axon regeneration (growth); ③ correct targeting by growing axons; and ④ establishment of correct and functional synaptic appositions. Cells transplanted to a lesion site play roles such as replacing lost cellular elements, secreting some neurotrophic factors to promote the regeneration (growth) of axons, bridging the gap in the injured spinal cord, modulating the inflammatory response after injury, and so on.

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STEM CELLS AND NEURAL STEM CELLS

Stem cells have the potential to differentiate into different cell types and self-renew for a long period of time. Many types of stem cells have been used in various experimental animal models of spinal cord injury to reduce deficits and improve functional recovery, such as embryonic stem cells, hematopoietic stem cells, and marrow stromal cells(MSCs)[1,2]. Their effects may be due to their capability to differentiate into neurons and some other gliocytes to replace lost neurons, secreting various neurotrophic factors, cytokines and biologically active factors to promote axons regeneration, and establishing functional synapses with the host. How to induce MSCs to differentiate into neural stem cells is one of the focuses of recent research.

Neural stem cells(NSCs), derived from mammalian embryonic brain, placed under a layer of endyma of the injured spinal cord of adult mammal, or multipotential stem cells[3], can self-replicate, secrete various neurotrophic factors and differentiate into neurons, astrocytes and oligodendrocytes.

Gao *et al*[4] transplanted primed human fetal neural stem cells(hNSCs) into spinal cords of sciatic nerve severed rats. Some of them differentiated into cholin-

ergic motoneurons that sent axons to contact medial gastrocnemius myocytes. Electromyogram and the gait of transplanted animals were much improved. This finding proved stem cell transplants are useful for motoneuron loss.

Pallini *et al*[5] found that NSC-derived astrocytes expressed vimentin when placed in injured spinal cord, suggesting that these cells differentiated as immature astrocytes, which permits axons to grow though the scar. Thus if we modify an astroglial scar with NSCs, the scar may no longer be a barrier to axon growth. Oligodendrocytes differentiate from NSCs and may be helpful for the remyelination of injured axons.

In addition, one study[6] found that grafted NSCs can protect host motoneurons around them. This may be a function of their secretion of neuro-protective factors. At present, there is limited information on how to induce NSCs to differentiate into certain cell types. In the future, more research needs be performed on the development and differentiation of NSCs, to explore their gene expression and signal conduction, and their accommodation during the differentiation process. More information is also needed about the mechanism of their multipotency and self-renewal, and the signals underlying their differentiation. The ultimate goal is that one day we will be able to induce NSCs to differentiate into the desired cell types.

SCHWANN CELLS

Schwann cells(SCs) are typical gliacytes in the peripheral nervous system(PNS). They form the myelin sheath around the axons and are involved in axon regeneration in the PNS.

Animal experiments[7] have proved that SCs can be used in the repair of central lesions. This may be due to their ability to promote axonal and myelin regeneration[8]. Correlative research found that neurotrophic factors, the extracellular matrix and adhesion molecules[9,10] expressed by Schwann cells can be used to improve the glial environment after SCI, and promote axon regeneration. In addition, many SC-derived factors can attenuate the effect of some axonal regeneration-inhibition factors by antagonizing Nogo receptor(NgR) binding with its ligands, and thus promote axon regeneration[11].

It is believed that the astroglial scar plays a dominant role in preventing CNS axon regeneration, by blocking axons from growing through it to regions on the other side. The invading SCs have difficulty migrating to the astroglial domain to integrate with host oligodendrocytes and astrocytes, so they are unable to provide a bridge for new-born axons to grow through the astroglial scar[9]. More research is needed on maintaining the biological activity of SCs and increasing their migration after being transplanted into the CNS. Based on this view, Papastefanaki et al[12] altered the adhesive properties of SCs by expressing the polysialylated(PSA) form of the neural cell adhesion molecule(NCAM) on their surface. Engineered SCs have an improved ability to associate with astrocytes in vitro. When these cells were transplanted into an in vivo mouse SCI model they promoted faster and significantly greater functional recovery when compared to SCI mice transplanted with normal SCs or no cells at all.

In another study, Woodhoo *et al*[13] implanted Schwann cell precursors into injured spinal cord. They found these cells have a greater ability to survive and migrate in the astroglial environment than normal SCs. The ability of SCs to repair CNS lesions may be enhanced when they are combined with some other therapeutic measure, such as increasing their secretion of neurotrophic factors by genetic engineering, filling in the gap and providing channels through the area of injured spinal cord with stents, and so on.

OLFACTORY ENSHEATHING CELLS

Olfactory ensheathing cells(OECs) are found along the full length of the olfactory nerve, crossing the peripheral nervous system-central nervous system junction. They have the ability to grow in the mature individual. Like SCs, OECs can promote axonal growth, in part through cell adhesion molecules, extracellular matrix, and possibly by secretion of neurotrophic growth factors that support axonal elongation and extension. They are also believed to support axonal remyelination, but this effect has been questioned[14].

Compared with other cells, OECs have a greater ability to migrate to areas distal from the transplanted site[15] and grow though the astroglial scar[16]. This allows the OECs to bridge the gap between lesion site and normal spinal cord, and the axons can grow along with them. Individuals can be transplanted with their own OECs to avoid the problems of immunological rejection and immunosuppression.

Correlated animal experiments suggested that OECs should not be transplanted in the early stage of acute SCI, and delaying transplantation after SCI may be beneficial to ensheathing cell survival[17]. Recently, there have been clinical reports about autologous OEC transplantation to treat human spinal cord injury[18]. Researchers concluded that transplantation of autologous OECs into the injured spinal cord is feasible and is safe, based on a one year post-implantation follow-up, despite the fact that there was no conspicuous recovery of sensory and motor functions.

In contrast to SCs, OECs have more potential

advantages. But research on OECs has not been as extensive as that on SCs, and more basic research is required to establish the mechanisms by which they promote axons regeneration. Recent research findings suggest that we can enhance the beneficial effect of OECs by employing genetic engineering[19] or transplanting them with some other cells, such as SCs.

MACROPHAGES AND FIBROBLASTS

After a CNS lesion, macrophages, which have both beneficial and harmful components, play a critical role in the secondary inflammatory reaction. Mantovani *et al*[20] found that macrophages could change into the classically-activated form or alteratively-activated forms when regulated with different signals in the inflammatory microenvirment. The classically-activated form (exhibiting a Th 1-like phenotype) could increase inflammatory damage to host cells. On the opposite side, the alteratively-activated form(exhibiting a Th 2 like-phenotype) could regulate the inflammatory reaction, clear away dead cells, promote blood vessels regeneration and tissue re-establishment, and thus provide an environment conducive to regeneration. Instead of replacing lost neural cells or secreting some neurotrophic factors, transplanting macrophages to a lesion site is an entirely different approach to promote axon regeneration. How to induce macrophages to change to the alteratively-activated form is a current area of active research.

Fibroblasts derived from the meninges overlying the cerebral cortex have also been transplanted by Franzen and his coworkers[21] into the injured adult rat spinal cord with the intention of reproducing a fibroadhesive scar. An unexpected finding that emerged from this study was that the transplanted fibroblasts promoted the regeneration of peptidergic axons originating from dorsal root afferents and, to a lesser extent, of supraspinal serotonergic fibers at the periphery of the grafts. The axonal promoting effect was thought to be at least partially due to their synthesis of neurotrophic factors. They could also remove some axons regeneration-inhibitors, such as reducing the formation of posttraumatic spinal cord cysts and astroglial scar. Modifing fibroblasts using genetic engineering to synthesize high-level neurotrophic factors has achieved good results.

OTHER CELLS

Besides the above cells, there are some other cells that can be used in cellular transplantation after SCI, such as cord blood $CD34^+$ cells, and microgliaschromaffin cells.

THE FUTURE

Cellular transplantation studies in experimental SCI models have shown that the opportunity for enhancing axonal growth, replacing dead cellular elements, and reversing demyelination after injury may be more extensive than previously thought. But there is still a long way to go before the basic research can be applied clinically. Despite considerable progress in recent years, the underlying mechanisms responsible for the failure of axonal regeneration after SCI remain only partially understood. Perhaps an integrative approach that combines several strategies, such as cellular transplantation of specific cell types or a combination of several cell types, neuroprotective interventions to attenuate secondary damage after SCI, and neurotrophin administration, will be more successful than any single approach in promoting recovery and thus reversing the human tragedy of SCI. Besides, we should do more studies on high-mammal such as pigs, dogs, even non-human primates, rather than rats, to make sure that cellular transplantation is safe and feasible for humans.

Reference

[1] McDonald JW, Liu XZ, Qu Y, Liu S, Mickey SK, Turetsky D, *et al*. Transplanted embryonic stem cells survive, differentiate and promote recovery in injured rat spinal cord. *Nature Medicine* 1999;5:1410-2.

[2] Koda M, Okada S, Nakayama T, Koshizuka S, Kamada T, Nishio Y, *et al*.Hematopoietic stem cell and marrow stromal cell for spinal cord injury in mice. *Neuroreport* 2005;16: 1763-7.

[3] Joannides AJ, Webber DJ, Raineteau O, Kelly C, Irvine KA, Watts C, *et al*. Environmental signals regulate lineage choice and temporal maturation of neural stem cells from human embryonic stem cells. *Brain* 2007; 130(5):1263-75.

[4] Gao J, Coggeshall RE, Chung J, Wang JG,Wu P.Functional motoneurons develop from human neural stem cell transplants in adult rats. *Neuroreport* 2007; 18:565-9.

[5] Pallini R , Vitiani LR,Bez A, Casalbore P, Facchiano F, Di Giorgi Gerevini V,*et al*. Homologous transplantation of neural stem cells to the injured spinal cord of mice. *Neurosurgery* 2005;57:1014-5.

[6] Ferrer-Alcon M, Winkler-Hirt C, Perrin FE, Kato AC.Grafted neural stem cells increase the life span and protect motoneurons in pmn mice. *Neuroreport* 2007; 18:1463-8.

[7] Dinh P, Bhatia N, Rasouli A, Suryadevara S, Cahill K, Gupta R.Transplantation of Preconditioned Schwann Cells Following Hemisection Spinal Cord Injury. *Spine* 2007;32:943-9.

[8] Gilson JM, Blakemore WF.Schwann cell remyelination is not replaced by oligodendrocyte remyelination following ethidium bromide induced demyelination. *Neuroreport* 2002; 13: 1205-8.

[9] Buss A, Pech K, Kakulas BA, Martin D, Schoenen J, Noth J, *et al*. Growth-modulating molecules are associated with invading Schwann cells and not astrocytes in human traumatic spinal cord injury. *Brain* 2007; 130:940-53.

[10] Frostick SP, Yin Q, Kemp GJ. Schwann cells, neurotrophic factors, and peripheral nerve regeneration. *Microsurgery* 1998; 18:397-405.

[11] Ahmed Z, Suggate EL, Brown ER, Dent RG, Armstrong SJ,

Barrett LB,*et al*.Schwann cell-derived factor-induced modulation of the NgR/p75NTR/EGFR axis disinhibits axon growth through CNS myelin in vivo and in vitro. *Brain* 2006;129: 1517-33.

[12] Papastefanaki F, Chen J, Lavdas AA, Thomaidou D, Schachner M, Matsas R.Grafts of Schwann cells engineered to express PSA-NCAM promote functional recovery after spinal cord injury. *Brain* 2007;130:2159-74.

[13] Woodhoo A, Sahni V, Gilson J, Setzu A, Franklin RJ, Blakemore WF, *et al*. Schwann cell precursors: a favourable cell for myelin repair in the Central Nervous System. *Brain* 2007; 130: 2175-85.

[14] Rizek PN, Kawaja MD.Cultures of rat olfactory ensheathing cells are contaminated with Schwann cells. *Neuroreport* 2006; 17:459-62.

[15] Li Y, Yamamoto MM, Raisman G, Choi D, Carlstedt T.An experimental model of ventral root repair showing the beneficial effect of transplanting olfactory ensheathing cells. *Neurosurgery* 2007; 60:734-41.

[16] Ram ón-Cueto A, Plant GW, Avila J, Bunge MB. Long distance axonal regeneration in the transected adult rat spinal cord is promoted by olfactory ensheathing glia transplants. *Neurosci* 1998; 18:3802-15.

[17] Woodhouse A, Vincent AJ, Kozel MA, Chung RS, Waite PM, Vickers JC, *et al*.Spinal cord tissue affects ensheathing cell proliferation and apoptosis. *Neuroreport* 2005;16:737-40.

[18] Feron F, Perry C, Cochrane J, Licina P, Nowitzke A, Urquhart S,*et al*. A. Autologous olfactory ensheathing cellular transplantation in human spinal cord injury. *Brain* 2005; 128:2951-60.

[19] Ruitenberg MJ, Levison DB, Lee SV, Verhaagen J, Harvey AR, Plant GW,NT-3 expression from engineered olfactory ensheathing glia promotes spinal sparing and regeneration. *Brain* 2005; 128:839-53.

[20] Mantovani A, Sozzani S, Locati M, Allavena P, Sica A. Macrophage polarization: tumor-associated macrophages as a paradigm forpolarized M2 mononucle arphagocytes. *Trends Immunol* 2002;23:549-55.

[21] Franzen R, Martin D, Daloze A, Moonen G, Schoenen J.Grafts of meningeal fibroblasts in adult rat spinal cord lesion promote axonal regrowth. *Neuroreport* 1999; 10:1551-6.